

Influence of ketanserin on experimental loss of renal blood flow autoregulation

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Influence of ketanserin on experimental loss of renal blood flow autoregulation. Serotonin is important for effective renal blood flow (RBF) autoregulation in the normal rat and at two or seven days of reperfusion following renal ischemia. It has been suggested that after these reperfusion periods and during renal perfusion pressure (RPP) lowering, the vasodilatory autoregulation mechanism is not damaged but overwhelmed by increased 5-HT₂-mediated vasoconstriction, resulting in complete loss of autoregulation. This study analyzes the influence of the 5-HT₂-antagonist ketanserin on RBF autoregulation after two hours or one day of renal reperfusion following ischemia and in a model of cyclosporine (20 mg/kg.day for 10 days)-induced nephrotoxicity. Autoregulation was lost both after brief reperfusion periods and after cyclosporine. Similar to the two or seven days of reperfusion experiments, ketanserin in the cyclosporine model led to reappearance of autoregulation down to RPP 95 mm Hg. Despite an increased response to intrarenal serotonin after two hours of reperfusion, autoregulation was not restored by ketanserin. At one day of reperfusion and with ketanserin, autoregulation was present down to 105 mm Hg. Thus, during the early reflow period, other factors (of decreasing importance) most likely add to autoregulation loss.

A well-known and important characteristic of regulation of renal function is autoregulation of renal blood flow (RBF) and glomerular filtration rate (GFR). RBF autoregulation is due largely to myogenic responses in preglomerular arteries [1, 2]. Within the autoregulatory renal perfusion pressure (RPP) range, vasodilation maintains RBF when RPP is lowered.

Serotonin [5-hydroxytryptamine (5-HT)], whether released from aggregating platelets or formed locally in the kidney or from an exogenous source, can modulate the contractile activity of vascular smooth muscle cells (VSMCs) [3]. Serotonergic 5-HT₂ receptors are present on VSMCs, and their activation leads to vasoconstriction; the endothelial 5-HT₁ receptor is involved in the release of nitric oxide and elicits vasodilation [4]. The 5-HT₂-receptor

blocker ketanserin [5] not only increases RBF and GFR in normal rats, but also preserves RBF autoregulation to RPPs as low as 70 to 75 mm Hg [6], far below the normal limit of 90 to 95 mm Hg. In the split hydronephrotic rat kidney, basal preglomerular 5-HT₂ vasoconstriction activity is present, and 5-HT administration impairs GFR autoregulation [7]. These data indicate that 5-HT₂ receptor activation is important for regulation of normal rat renal hemodynamics and led us to study the potential role of 5-HT in the loss of autoregulation after renal ischemia or cyclosporine-induced nephrotoxicity.

In patients [8] and in models of experimental acute renal failure (ARF) induced by renal artery occlusion [9] or intrarenal norepinephrine [9, 10], even short insults of subsequent renal hypoperfusion after ischemic ARF led to recurrent renal damage. Lack of RBF autoregulation, hence of protection against repeated falls in RPP, may play a role in these successive insults. Loss of RBF autoregulation has been reported in some models of postischemic ARF [11, 12] and in some animal models of subchronic cyclosporine treatment [13, 14]. Cyclosporine-induced renal dysfunction is due primarily to hemodynamic effects resulting in a fall of RBF and GFR [15]. The loss of autoregulation in cyclosporine-induced ARF makes the kidney vulnerable to hypoperfusion damage and hence to ischemia. A contribution of ischemia to cyclosporine-induced renal damage has been suggested [16–18].

KETANSERIN AND AUTOREGULATION IN POSTISCHEMIC CONDITIONS

Renal blood flow autoregulation is lost in rats at two- or seven days of reperfusion after 40-minutes unilateral renal artery clamping. Acute administration of ketanserin restores autoregulation at both times but does not ameliorate the fall in GFR or influence fractional sodium excretion [11]. Although ketanserin also has α_1 -adrenergic blocking characteristics [6, 11, 19], the dose used in our studies in normal [6] or postischemic rats (0.05 mg/kg i.v. bolus, followed by 0.1 mg/kg.hr infusion) [11] was devoid of α_1 -blocking actions. These studies imply that the vasodilatory autoregulation mechanism *per se* is not impaired but

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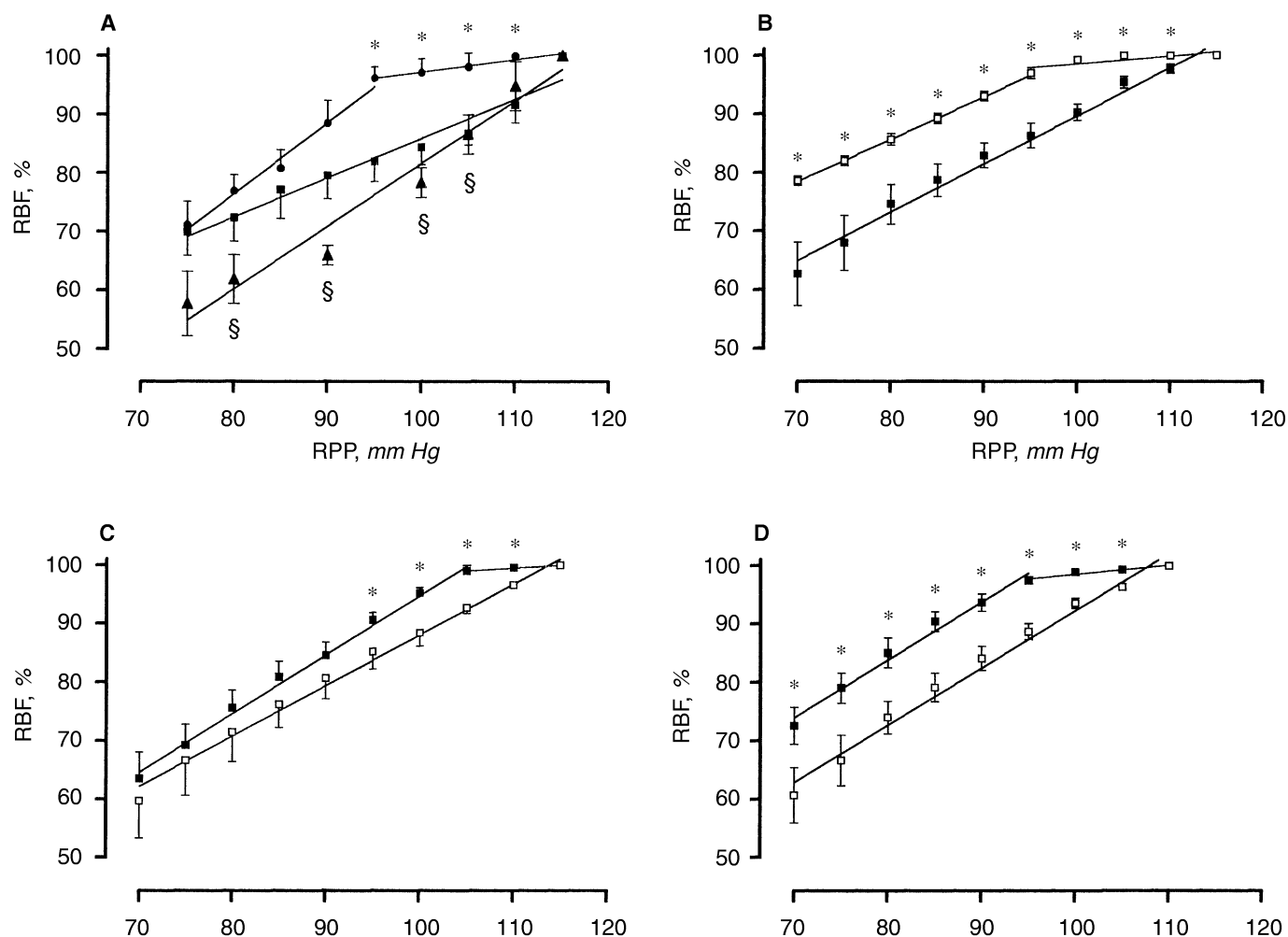


Fig. 1. Renal blood flow (RBF; percentage of initial flow) as a function of renal perfusion pressure. Means \pm SEM. (A) Control autoregulation curve (●) before 40-minutes unilateral renal artery clamping (ischemia; RBF 5.15 \pm 0.58 ml/min at 115 mm Hg), at two days of reperfusion (■; RBF 4.08 \pm 0.65 ml/min at 115 mm Hg), at two days of reperfusion and verapamil (▲; RBF 4.85 \pm 0.7 ml/min at 115 mm Hg; N = 6). * P < 0.05 control versus two days of reperfusion. § P < 0.05, control versus two days of reperfusion and verapamil. (B) Control autoregulation curve (□) before ischemia (RBF 4.75 \pm 0.28 ml/min at 115 mm Hg), at two hours of reperfusion and ketanserin (■; RBF 3.69 \pm 0.29 ml/min at 115 mm Hg; N = 6). * P < 0.05, control versus two hours of reperfusion. (C) At one day of reperfusion before ketanserin (□; RBF 3.58 \pm 0.16 ml/min at 115 mm Hg), after ketanserin (■; RBF 3.78 \pm 0.18 ml/min at 115 mm Hg; N = 5). * P < 0.05, before versus after ketanserin. (D) In cyclosporine-treated rats before ketanserin (□; RBF 3.59 \pm 0.24 ml/min at 110 mm Hg), after ketanserin (■; RBF 3.95 \pm 0.35 ml/min at 110 mm Hg; N = 8). * P < 0.05, before versus after ketanserin. Curves were obtained All comparisons on a point-to-point basis.

that autoregulation is rather suppressed by enhanced 5-HT₂ influence at two or seven days of reflow. 5-HT might thus be an important determinant of the effective autoregulation range, both in control rats and after experimental renal ischemia/reperfusion damage [11].

To understand better the beneficial influence of ketanserin on autoregulation loss in the renal artery clamp model, the possible importance of Ca²⁺ has been explored. As well as structural vascular alterations such as VSMC necrosis [11, 12, 20], adventitial fibrosis [12], hypersensitivity to renal nerve stimulation [20], and loss of response to endothelium-dependent vasodilators [20], accumulation of Ca²⁺ in VSMCs could cause aberrant renovascular function in postischemic conditions [21]. Two chemically dis-

similar Ca²⁺ entry blockers, verapamil and diltiazem, have beneficial effects on autoregulatory responses after norepinephrine-induced ischemic ARF [21].

We thus examined the influence of verapamil on RBF autoregulation loss two or seven days after ischemia. After confirming loss of autoregulation, verapamil was given i.v. (0.8 mg/kg bolus plus 20 μ g/kg.min infusion) or intrarenally (i.r. infusion of 4 μ g/kg.min; that is, the maximal dose without systemic effects). Preliminary experiments showed that the i.v. dose significantly attenuated but did not block the vasoconstrictor response to i.r. phenylephrine or 5-HT, with minimal alteration of mean arterial pressure. After one hour of verapamil, another autoregulation curve was obtained, while the infusion was continued. Figure 1A

shows the changes in RBF in response to progressive RPP reduction in controls and at two days of reperfusion before and after i.v. administration of verapamil. Verapamil significantly increased basal RBF, but RBF autoregulation was still absent. Similar results were obtained at seven days of reflow and after i.r. verapamil (not shown). These results are contrary to those from the norepinephrine model [21]. The fact that the latter is characterized predominantly by functional endothelial damage, whereas a renal artery clamp model is characterized mainly by morphological and functional VSMC damage, might help explain this discrepancy [20].

The question remained whether the 5-HT₂-mediated influence on the expression of RBF autoregulation, found in control kidneys as well as two or seven days postischemia, is also present at shorter reperfusion periods. In conscious rats, the 5-HT₂-antagonistic activity of levomepamil improved renal function after a rather brief reperfusion period following ischemia [23]. We thus examined RBF autoregulation and the influence of ketanserin at two hours or one day following unilateral renal artery clamping. After two hours of reflow, RBF autoregulation was absent in all animals and was not restored by ketanserin (given for 1 hr; Fig. 1B). However, i.r. 5-HT injection elicited a significantly greater RBF decrease, implying increased 5-HT₂-mediated vasoconstriction at two hours of reperfusion. These data suggest that perhaps other factors are responsible for autoregulation loss in this early reperfusion period.

Autoregulation was still completely absent after ischemia and one day of reperfusion. A one hour of ketanserin administration partly restored autoregulation: The percentage RBF improved significantly for RPPs between 110 and 95 mm Hg. Contrary to the two hours of reperfusion, which showed no plateau, regression analysis of the data one day after ischemia and with ketanserin showed a plateau between 115 and 105 mm Hg (Fig. 1C). Taken together, it seems that the impact of unknown factors suppressing autoregulation at two hours of reflow becomes less important with longer reperfusion. Only after two days of reperfusion is an autoregulation setpoint of 95 mm Hg apparent after 5-HT₂-antagonism, as found previously [11].

KETANSERIN AND AUTOREGULATION AFTER CYCLOSPORINE TREATMENT

5-HT may also be important in alterations of renal hemodynamics seen after cyclosporine [24]. Simultaneous administration of cyclosporine with ketanserin protects renal function [25], although ketanserin's possible influence on the loss of autoregulation after cyclosporine was not considered.

We thus examined the effect of ketanserin on the loss of autoregulation in cyclosporine-induced nephrotoxicity (20 mg cyclosporine/kg/day orally for 10 days, leading to a lowered RBF and GFR) [14]. At day 11, RBF autoregulation

was lost in all animals. Ketanserin acutely restored RBF autoregulation (Fig. 1D) as after renal ischemia [11]. Thus, in this nephrotoxic model also, the vasodilatory autoregulation mechanism itself seems not to be impaired, but is rather overwhelmed by a stronger vasoconstriction that can be abolished by ketanserin.

In conclusion, 5-HT seems to influence the effective range of RBF autoregulation in the normal rat kidney. It is even more important in experimental ARF following ischemia by renal artery clamping and in a model of subchronic cyclosporine treatment, although it may not be the sole factor suppressing RBF autoregulation. The persistent renal postischemic vasoconstriction is diminished by Ca²⁺ antagonists, but in the renal artery clamp model at least, RBF autoregulation at two- or seven days of reperfusion could not be restored.

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